

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215383Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215383
PDUFA Goal Date	September 15, 2021
OSE RCM #	2021-51, 2021-55
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	August 10, 2021
Subject	Evaluation of Need for a REMS
Established Name	Belzutifan
Trade Name	Welireg
Name of Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Therapeutic Class	hypoxia-inducible factor inhibitor
Formulation(s)	40 mg tablet
Dosing Regimen	belzutifan 120 mg orally once daily

Table of Contents

EXECUTIVE SUMMARY	3
1 Introduction.....	3
2 Background	3
2.1 Product Information.....	3
2.2 Regulatory History	4
3 Therapeutic Context and Treatment Options	4
3.1 Description of the Medical Condition.....	4
3.2 Description of Current Treatment Options	4
4 Benefit Assessment.....	4
5 Risk Assessment & Safe-Use Conditions.....	5
5.1 Anemia.....	5
5.2 Hypoxia	6
5.3 Embryo-Fetal Toxicity	6
6 Expected Postmarket Use	6
7 Risk Management Activities Proposed by the Applicant.....	7
8 Discussion of Need for a REMS.....	7
9 Conclusion & Recommendations	7
10 Appendices	8
10.1 References.....	8

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Welireg (belzutifan) is necessary to ensure the benefits outweigh its risks. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted a New Drug Application (NDA) 215383 for belzutifan with the proposed indication for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. The serious risks associated with belzutifan include anemia, hypoxia, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan.

DRM and Division of Oncology 1 (DO1) agree that a REMS is not necessary to ensure the benefits of belzutifan outweigh its risks. The efficacy of belzutifan was supported by Study MK-6482-004, in which the belzutifan group had an overall response rate (ORR) of 49.2% for VHL disease-associated RCC. In addition, the belzutifan group had an ORR of 83.3% for pancreatic neuroendocrine tumors and ORR of 62.5% for CNS hemangioblastomas. Labeling that includes a boxed warning and a Medication Guide will be used to communicate the serious risk of embryo-fetal toxicity. The other serious risks including anemia and hypoxia will be communicated in the warnings and precautions section of the label.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Welireg (belzutifan) is necessary to ensure the benefits outweigh its risks. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted a New Drug Application (NDA) 215383 for belzutifan with the proposed indication for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.¹ This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Welireg (belzutifan), a NME, is a hypoxia-inducible factor inhibitor, proposed for treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery. Belzutifan is supplied as a 40 mg tablet. The proposed dosing regimen is 120 mg orally once daily until disease progression or unacceptable toxicity.^b Belzutifan is not currently approved in any jurisdiction. Belzutifan was granted orphan drug designation and breakthrough therapy.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for belzutifan NDA 215383 relevant to this review:

- 06/24/2020: Orphan drug designation granted
- 07/23/2020: Breakthrough therapy designation granted
- 01/15/2021: NDA 215383 submission for treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery received
- 07/14/2021: A Post Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for belzutifan.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Von Hippel-Lindau disease is an autosomal dominant syndrome that is associated with the development of benign and malignant tumors.^{2,3,4} The incidence of VHL disease is approximately 1 in 36,000 livebirths.^{2,4,c} Patients with VHL disease may develop tumors in the central nervous system, kidneys, adrenal glands, pancreas, and reproductive organs.² Complications due to RCC and CNS hemangioblastomas are a main cause of mortality in VHL disease.^{4,5,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The management of patients with VHL disease requires a multidisciplinary approach.^{2,3,4} Currently, there are no FDA approved drugs for the treatment of VHL disease-associated RCC.⁵ In patients with RCC tumors ≥ 3 cm, nephron-sparing surgery is recommended to prevent metastasis.^{4,5,6}

4 Benefit Assessment

The pivotal trial NCT 03401788 (Study MK-6482-004) supporting this application for efficacy and safety consisted of a Phase 2, open-label trial which evaluated belzutifan in patients with VHL-associated RCC diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney.^{1,5,7} Patients (N=61) received belzutifan 120 mg orally once daily. The primary endpoint was overall response rate (ORR) for VHL disease-associated RCC. The belzutifan group had an ORR of 49.2% (95% CI 36.1% to 62.3%) with a duration of response which ranged from 2.8+ to 22.3+ months. One of

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

the secondary endpoints was ORR for VHL disease-associated non-RCC tumors. The belzutifan group had an ORR of 83.3% (95% CI 51.6% to 97.9%) for pancreatic neuroendocrine tumors (N=12) and ORR of 62.5% (95% CI 40.6% to 81.2%) for CNS hemangioblastomas (N=24). The FDA clinical reviewer recommended approval based on the currently available data.^e

5 Risk Assessment & Safe-Use Conditions

The safety of belzutifan was evaluated in NCT 03401788 (Study MK-6482-004).^{1,5,7,f} In the safety population from this clinical trial, 61 patients received belzutifan. Discontinuation due to adverse reactions occurred in 3.3% in the belzutifan group. Common adverse reactions reported with belzutifan included decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

The serious risks^g associated with belzutifan of anemia, hypoxia, and embryo-fetal toxicity are summarized in the section below.

5.1 ANEMIA

Section 5.1 of the draft labeling states belzutifan may cause severe anemia that may require blood transfusion. An adverse reaction of anemia occurred in 90% of patients in the belzutifan group, with Grade 3 anemia reported in 7% of patients in Study MK-6482-004. Study MK-6482-001 (NCT 02974738) was a Phase 1 study in patients with advanced solid tumors. An adverse reaction of anemia occurred in 76% of patients in the belzutifan group (120 mg once daily group, N=58), with Grade 3 anemia reported in 28% of patients in Study MK-6482-001.

The proposed label recommends to monitor for anemia before initiation and periodically throughout treatment with belzutifan and to closely monitor patients who are dual UGT2B17 and CYP2C19 poor metabolizers due to potential increases in exposure that may increase the incidence or severity of anemia. It recommends to transfuse patients as clinically indicated. The proposed label also recommends for patients with hemoglobin(Hb)<9 g/dL to withhold belzutifan until ≥ 9 g/dL then resume

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

^g Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

at reduced dose or permanently discontinue belzutifan depending on the severity of anemia and for patients with life threatening anemia or when urgent intervention is indicated to withhold belzutifan until $Hb \geq 9$ g/dL, then resume at a reduced dose or permanently discontinue belzutifan. Section 5.1 of the draft labeling also states that the use of erythropoiesis stimulating agents (ESAs) for treatment of anemia is not recommended in patients treated with belzutifan and for patients treated with belzutifan who develop anemia, the safety and effectiveness for use of ESAs has not been established. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 HYPOXIA

Section 5.2 of the draft labeling states belzutifan may cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization. An adverse reaction of hypoxia occurred in 1.6% of patients in the belzutifan group in Study MK-6482-004. In addition, an adverse reaction of hypoxia occurred in 29% of patients in the belzutifan group (120 mg once daily group, N=58), with Grade 3 hypoxia reported in 16% of patients in Study MK-6482-001.

The proposed label recommends to monitor oxygen saturation before initiation and periodically throughout treatment with belzutifan. It recommends for decreased oxygen saturation with exercise (pulse oximeter $<88\%$ or $P_aO_2 \leq 55$ mm Hg) to consider withholding belzutifan until pulse oximetry with exercise is greater than 88%, then resume at the same dose or at a reduced dose. The proposed label also states for decreased oxygen saturation at rest (pulse oximeter $<88\%$ or $PaO_2 \leq 55$ mm Hg) or urgent intervention indicated to withhold belzutifan until resolved and resume at a reduced dose or discontinue. It also recommends permanent discontinuation for life-threatening hypoxia or for recurrent symptomatic hypoxia. Section 5.2 of the draft labeling also states to advise patients to report signs and symptoms of hypoxia immediately to a healthcare provider. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 EMBRYO-FETAL TOXICITY

Belzutifan may cause fetal harm based on animal studies. No clinical data is available with belzutifan in pregnancy in humans. The risk of embryo-fetal toxicity will be included in a boxed warning, a Medication Guide, and the warnings and precautions section of the label. The proposed label states to advise pregnant women and females of reproductive potential of the potential risk to the fetus. In females of reproductive potential, the proposed label recommends to verify pregnancy status before starting belzutifan and that effective non-hormonal contraception be used during treatment and for 1 week after the last dose. The boxed warning in the draft labeling states belzutifan can render some hormonal contraceptives ineffective. Coadministration of belzutifan with CYP3A4 substrates decreases concentrations of CYP3A substrates which may reduce the efficacy of these substrates. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for 1 week after the last dose.

6 Expected Postmarket Use

If approved, belzutifan will primarily be used in both inpatient and outpatient settings. The likely prescribers will be oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for belzutifan beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of belzutifan on the basis of the efficacy and safety information currently available. Currently, there are no FDA approved drugs for the treatment of VHL disease-associated RCC. The efficacy of belzutifan was supported by Study MK-6482-004, in which the belzutifan group had an ORR of 49.2% for VHL disease-associated RCC. In addition, the belzutifan group had an ORR of 83.3% for pancreatic neuroendocrine tumors and ORR of 62.5% for CNS hemangioblastomas. The serious risk associated with belzutifan of embryo-fetal toxicity will be communicated in a boxed warning, a Medication Guide, and in the warnings and precautions section of the label. The other serious risks including anemia and hypoxia will be communicated in the warnings and precautions section of the label.

Von Hippel-Lindau disease is an autosomal dominant syndrome that is associated with the development of benign and malignant tumors. The incidence of VHL disease is approximately 1 in 36,000 livebirths. Patients with VHL disease may develop tumors in the central nervous system, kidneys, adrenal glands, pancreas, and reproductive organs. Complications due to RCC and CNS hemangioblastomas are a main cause of mortality in VHL disease. Based on the efficacy and risk associated with belzutifan for treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery, the DRM and DO1 recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with belzutifan. Labeling that includes a boxed warning will be used to communicate the serious risk of embryo-fetal toxicity. The boxed warning states exposure to belzutifan during pregnancy can cause embryo-fetal harm and to verify pregnancy status prior to the initiation of belzutifan. Advise patients of these risks and the need for effective non-hormonal contraception. Belzutifan can render some hormonal contraceptives ineffective.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore a REMS is not necessary for belzutifan to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ Proposed prescribing information for belzutifan as currently edited by FDA, last accessed August 10, 2021.

² Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003;361(9374):2059-67.

³ Schmid S, Gillessen S, Binet I, et al. Management of von hippel-lindau disease: an interdisciplinary review. *Oncol Res Treat*. 2014;37(12):761-71.

⁴ Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A Review of Von Hippel-Lindau Syndrome. *J Kidney Cancer VHL*. 2017;4(3):20-29.

⁵ Fallah J, Brave M, Gittleman H, Bloomquist E, Weinstock C. Division of Oncology 1 (DO1). Belzutifan (MK6482). Mid-Cycle Meeting, clinical and statistics reviewer slides. April 6, 2021.

⁶ Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. MK-6482. Module 2.5. clinical overview. January 15, 2021.

⁷ Belzutifan multi-disciplinary review and evaluation. Accessed July 24, 2021.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
08/11/2021 07:41:58 AM

NAOMI S BOSTON
08/11/2021 11:08:34 AM

DORIS A AUTH
08/11/2021 11:58:05 AM